Proposed PCB Congener Groupings for Epidemiological Studies

Health effects related to polychlorinated biphenyls (PCBs), which include 209 possible congeners exhibiting a variety of chlorine substitution patterns (Fig. 1), are the subject of numerous research investigations. Individual members of this family evoke diverse responses in experimental models and in humans. Certain PCB congeners mimic hormones and are neurotoxic (*1–3*). Others produce a dioxinlike response, which has been attributed to steric homology with 2,3,7,8-tetrachlorodibenzodioxin (TCDD) (*4,5*). Epidemiologic studies have tended to report health effects expressed as the total of individual PCB congener levels or as the concentration relative to a commericial PCB mixture (e.g., Aroclor 1248, 1254, or 1260). However, as congener-specific analyses of serum, adipose tissue, and other media become routinely available, it is highly desirable to organize risk analysis along biologically plausible lines, thereby avoiding misclassification of exposure and strengthening the toxicologic associations.

One approach to interpreting PCBs in environmental materials is to group the dioxinlike PCB congeners together. With this method, a single index is computed as the sum of the congener concentrations weighted by their toxic equivalents relative to TCDD (*4,6*). However, analagous schema for estrogenic, neurotoxic, and cytochrome P450-inducing PCBs are not available at this time.

As a means of evaluating hormonal effects, Wolff and Toniolo (*7*) proposed a classification system based on structural, biological, and pharmacokinetic considerations. They assigned PCB congeners to three groups: estrogenic/neurotoxic, antiestrogenic (dioxinlike), and enzyme-inducing [phenobarbital (PB)-type cytochrome P450]. The desirability of developing such a system has been raised recently with respect to a number of ongoing research investigations that are attempting to relate exposure to organochlorines, including PCBs, with breast cancer risk (*8*). One of these studies, in which we are co-investigators, is determining levels of PCBs in house dust as well as blood, providing an opportunity to assess exposure using internal and external measurements. As a starting point for discussion and initial classification, we suggest one possible set of PCB functional groupings (see Table 1) based on existing literature (*1–8,11–13*) and structure-activity considerations.

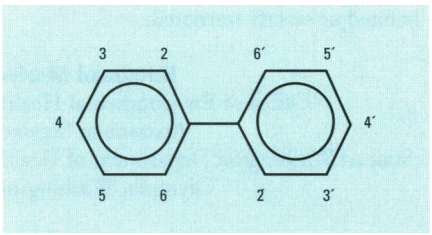

Figure 1. Polychlorinated biphenyl. Positions 2,3,4,5,6 and 2′,3′,4′,5′,6′ are substituted with H^- or Cl^-. Positions 2, 2′, 6, and 6′ bear *ortho*-substituents.

Table 1. Major[a] PCB peaks occurring in house dust or human samples

Humans and house dust			Human only			Dust only[b]		
	Chlorobiphenyl substitution			Chlorobiphenyl substitution			Chlorobiphenyl substitution	
BZ #[c]	Ring 1[d]	Ring 2	BZ #	Ring 1	Ring 2	BZ #	Ring 1	Ring 2
Group 1 (potentially estrogenic)								
Group 1A (weak phenobarbital inducers, estrogenic, not persistent)								
44	25	23				31	25	4
49	25	24				70	25	34
52	25	25						
Group 1B (weak phenobarbital inducers, persistent)								
101	25	245	174	236	2345			
187	2356?	245	177	2356?	234			
			201	2356?	2345			
Group 2 (potentially antiestrogenic and immunotoxic, dioxinlike)								
Group 2A: non-*ortho* and mono-*ortho* substituted (moderately persistent)								
66	34	24	126	34	345			
74	4	245	156	34	2345			
77	34	34	167	345	245			
105	34	234	169	345	345			
118	34	245						
Group 2B: di-*ortho* substituted (limited dioxin acitvity, persistent)								
128	234	234						
138	234	245						
170	234	2345						
Group 3 (phenobarbital, CYP1A and CYP2B inducers, biologically persistent)								
99	245	24	183	2346	245			
153	245	245						
180	2345	245						
196	2345	2346						
203	23456	245						

[a]Either 2% or more by weight of 65 congeners in dust and high percentage in humans, or demonstrated activity in one of the three groupings and present at 1% or more of 65 congeners in dust or commonly detected in humans.
[b]From Vorhees (*9*).
[c]BZ# is congener number as designated by Ballschmitter and Zell (*10*).
[d]Ring 1 structure signifies biological activity for class 1 and 2.

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DDT/DDE and Infant Exposure

The article by López-Carrillo et al. (*1*), which discusses the public health implications of using DDT in Mexico, is a welcome contribution to the literature. DDT is a public health concern not only in the countries still using the chemical but also in those countries that have restricted, phased out, or banned use of the chemical. Presently, it is difficult to conclude if DDT contributes to breast cancer incidence, and the lack of complete confidence in our understanding of the relationship between this xenoestrogen and breast cancer should not prevent us from finding alternatives to DDT that have less public health impact. López-Carrillo et al. (*1*) base their concern for DDT primarily on the possible increase of breast cancer with exposure. Although this endpoint is of concern, toxicological endpoints that deserve equal attention pertain to infant exposure.

Teratology studies by Eriksson et al. (*2–4*) have investigated neurological and developmental endpoints in neonatal mice. Although work is still required to elicit the nature of low-dose DDT damage to the central nervous system in neonates, the results of their work suggest that 1) the neonatal period of brain development may be similar to other perinatal periods in which the brain is susceptible to xenobiotic compounds and 2) susceptibility to damage by DDT and similar-acting compounds may be greatest during the height of rapid brain growth and during the rapid development of muscarinic acetylcholine receptors in the cerebral cortex (*2–5*).

Although a direct comparison between the 10-day-old mice used in these studies and 10-day-old humans cannot be made, the sequence of events of brain development between humans and rodents is quite similar (*6,7*) That is, nerve production, myelin formation, receptor development, etc., are events that occur in the same order in rodents and humans (*7*). At day 10, mice are in their last stages of neuron production for the hippocampus and cerebellum (*8*). Antimitotic drugs are much more toxic if exposure occurs earlier in development when more neurons are being produced (*9,10*). However, the first 2 weeks of postnatal life in the rodent are a period of rapid development of synaptic connections, transmitter systems, and myelination. During this stage of brain development, exposure to teratogens leads to disruption of some or all of these events, resulting in permanent injury. For example, metals such as lead, cadmium, and organotin can injure the brain at this stage, as can hypothyroidism (*11*). The applicability of these teratology study results to the human situation will continue to become clearer as future findings delineate effects at developmental time points when mice are more sensitive and when the development of rodent and human neurosystems are similar.

It was with the consideration of this previously described experimental work that a breast milk study was initiated in the state of Washington to access a population of concern consisting primarily of low-income Hispanics. We conducted this study to 1) determine actual levels of DDT and DDE in breast milk of mothers residing in the Yakima River basin; 2) assess the relative impact of fish consumption on the total DDT/DDE body burden; and 3) determine if total DDT and DDE levels received by breast-feeding infants were elevated to potentially deleterious levels. Fish collected from the Yakima River between 1989 and 1991 had DDT and DDE levels among the highest recorded in the United States (*12*). We were concerned that mothers who frequently consumed Yakima River bottom-feeding fish could have breast milk DDT and DDE concentrations sufficiently high to expose their infants to potentially deleterious levels of these compounds. Among the 36 individuals sampled (12 individuals for each of three cohorts: fish consumers, Mexico-born nonconsumers, and U.S.-born nonconsumers); results indicated that fish consumption did not significantly increase DDT/ DDE breast milk concentrations. However, as has been reported elsewhere, subjects born in Mexico had significantly elevated levels of DDT and DDE ($p < 0.01$) in breast milk compared to levels found in subjects born in the United States (*1,13,14*).

For each cohort sampled, an infant DDT intake level was determined using the breast milk value that included two-thirds of that particular cohort. For a 5-kg infant consuming 1 kg breast milk daily, infant DDT intake levels for the cohorts were in the range of $0.7–3.5 \times 10^{-3}$ mg/kg/day. These results do not include two outliers from the Mexico-born nonconsumer cohort who had DDT/DDE levels greater than two standard deviations from the mean. Our infant exposure values derived from the cohort data (excluding outliers) were more than two orders of magnitude below the administered dose used by Eriksson et al. (*2–4*). The two women (considered outliers) had DDT breast milk levels that correspond to the elevated levels observed in women living in Mexico. These DDT breast milk levels would expose breast-feeding infants each day to levels that are less than two orders of magnitude from the one-time administered dose given to neonatal mice.

Although DDT may contribute to an increase in breast cancer, exposure to DDT may also produce neurological and developmental endpoints of significance that require consideration. The study conducted in Washington State and data on breast milk DDT levels obtained from women in Mexico indicate that infants may be exposed to potentially deleterious levels of these compounds through breast milk. With DDT in our environment, various populations can still be exposed to sufficiently elevated DDT levels in the United States that warrant concern. Also, due to the influx of Mexico-born women into the United States, their U.S.-born infants may be a population of concern. Future research in this area should consider the feasibillty of detecting these neurological and developmental outcomes in individuals that have been previously exposed as infants, and not just for those living in areas where DDT is still in use but also in countries or areas where use has been banned or severly restricted.

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